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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/213,834	12/17/98	ROMANTCHIKOV Y	99999/400400

EXAMINER	

HM22/0313

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ART UNIT	PAPER NUMBER
1631	2

DATE MAILED: 03/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/213,834	Applicant(s) ROMANTCHIKOV, YURI (IOURI)	
	Examiner Stephen C Siu	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-16,18-21,24-30 and 41-50* is/are allowed.

6)☒ Claim(s) *22,23 and 31-40* is/are rejected.

7)☒ Claim(s) *17 and 23* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing". Applicant must provide: a substitute computer readable form copy of the Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Claim Objections

Claim 23 is objected to because of the following informalities: the claim contains an exponential with two hyphens, which appears to be erroneously typed. Appropriate correction is required.

Claim 17 recites "said 3' overhand" which appears to be a misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites "selected from the group consisting essentially of" which is confusing because it is not clear what is encompassed in the group with the use of the term "essentially".

Claim 23 recites "said first nucleic acid concentration can comprise about" which is confusing because it is not clear if the first nucleic acid concentration comprises the recited concentration or if it does not comprise but only has the capability of comprising the recited concentration. Also, 10^{-21} to about 10^{-14} mole is an amount rather than a concentration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 31-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Guegler (US Pat 5,844,084).

The claims are drawn to a nucleic acid insert or a cDNA library in a circular vector.

Guegler (US Pat 5,844,084) discloses a circular phagemid DNA molecule that includes all DNA sequences of a plasmid and a cDNA insert (col.9, lines 30-34).

Guegler anticipates the claimed invention because of the disclosure of a circular vector containing a nucleic acid/cDNA insert. The claimed invention as recited in claims 31 and 32 is drawn to the vector as prepared by a recited method. This is considered a product by process claim. It is brought to the Applicant's attention that a product by process claim is examined for novelty and obviousness of the claimed product only, and that no consideration is given to the novelty or obviousness of the method of making the claimed product. See M.P.E.P. 2113.

Claims 31-34 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Miki (Gene, 83 (1989), pp. 137-146) in light of Maniatis (Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, 1982).

The claims are drawn to a mixture of linear vectors joined to nucleic acid fragments with at least 95% of the nucleic acid fragments are inserted into circularized

vectors and at least 95% of the circularized vectors contain only one nucleic acid fragment insert. The claims are further drawn to a linear vector comprising cohesive circularization ends and an insertion site wherein each of the ends is at least 20 base pairs from the insertion site and are between 8 to 50 nucleotides in length and wherein ligase does not substantially covalently join the cohesive circularization ends.

Miki (Gene, 83 (1989), pp. 137-146) teaches a directional cloning system to construct cDNA libraries containing full-length inserts at high frequency in which a λpCEV vector with cohesive circularization ends is circularized, then cleaved to expose the sticky ends of the vector molecules for attachment with the insert, the insert site previously being distant from the cohesive circularization ends of the linearized vector and the restriction enzyme *Sfi*I being used to cleave the insert sites. Hybridization is produced automatically due to the base-pairing specificity indicating that ligase does not substantially covalently join the cohesive ends. The short sticky ends of the insertion ends are 3 nucleotides in length. The vector contains a virus cos site (see fig 2, page 141). The base pairs of the insertion site are located 20 base pairs from the cohesive circularization ends (see fig. 1, page 140). Miki teaches that certain restriction enzymes cleave the nonsymmetrical site yielding two different sticky ends. In this case, only these two sticky ends can be ligated. When a vector DNA containing two different sites with this feature is cleaved by restriction enzymes of this kind, the stuffer fragment hemmed by the sites removed, and ligation performed with inserts having sticky ends complementary to the vector's ends, all (i.e. 100%) of the clones obtained contain single

inserts in the defined orientation (page 142, col. 1, lines 13-23). The insert and vector are used to transform an E.coli strain (page 142, col.2, lines 10-14). It is well known in the art, as evidenced by Maniatis, that in the life cycle of the bacteriophage λ, upon entering the bacterial host as a linear duplex, the vector circularizes (page 19, figure 1.6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miki (Gene, 83 (1989), pp. 137-146) in view of Aslanidis (PCR Methods and Applications, Vol.4, No.3, Dec 1994, pp. 172-177).

The claims are drawn to a mixture of linear vectors joined to nucleic acid fragments with at least 95% of the nucleic acid fragments are inserted into circularized vectors and at least 95% of the circularized vectors contain only one nucleic acid fragment insert. The claims are further drawn to a linear vector comprising cohesive circularization ends and an insertion site wherein each of the ends is at least 20 base pairs from the insertion site and are between 8 to 50 nucleotides in length and wherein

ligase does not substantially covalently join the cohesive circularization ends. Also, a kit is claimed comprising the linearized vector as above.

Miki (Gene, 83 (1989), pp. 137-146) teaches a directional cloning system to construct cDNA libraries containing full-length inserts at high frequency in which a λpCEV vector with cohesive circularization ends is circularized, then cleaved to expose the sticky ends of the vector molecules for attachment with the insert, the insert site previously being distant from the cohesive circularization ends of the linearized vector and the restriction enzyme *Sfi*I being used to cleave the insert sites. Hybridization is produced automatically due to the base-pairing specificity indicating that ligase does not substantially covalently join the cohesive ends. The short sticky ends of the insertion ends are 3 nucleotides in length. The vector contains a virus cos site (see fig 2, page 141). The base pairs of the insertion site are located 20 base pairs from the cohesive circularization ends (see fig. 1, page 140). Miki teaches that certain restriction enzymes cleave the nonsymmetrical site yielding two different sticky ends. In this case, only these two sticky ends can be ligated. When a vector DNA containing two different sites with this feature is cleaved by restriction enzymes of this kind, the stuffer fragment hemmed by the sites removed, and ligation performed with inserts having sticky ends complementary to the vector's ends, all of the clones obtained contain single inserts in the defined orientation (page 142, col. 1, lines 13-23).

Miki does not explicitly teach the length of the nucleotide tail at the cohesive ends.

Aslanidis (PCR Methods and Applications, Vol.4, No.3, Dec 1994, pp. 172-177) teaches the minimal length requirement of single-stranded tails for ligation-independent cloning of nucleotides. Aslanidis demonstrates that the transformation efficiencies using 12-nucleotide cohesive ends produces four times more transformants than using 10-nucleotide cohesive ends and that the use of 8-nucleotide long tails resulted in no transformants (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a linearized vector comprising an origin of replication, a virus cos site, an insertion site of between 1 and 7 nucleotides in length and at least 20 base pairs from two complementary cohesive circularization ends, cleave the insertion site with at least one restriction enzyme and obtain a mixture formed from a joining reaction of a population of the linearized vectors with nucleic acid fragments such that at least 95% of the nucleic acid fragments are inserted into circularized vectors and at least 95% of the circularized vectors contain only one nucleic acid fragment as per the teachings of Miki and further to utilize a vector with cohesive circularization ends of specifically about 8 to about 50 nucleotides in length because using 10 or 12 nucleotide cohesive ends produced improved (up to 4 times improved) transformation efficiencies but no increase in transformation efficiency occurs with cohesive ends less than 8 nucleotides in length as per the teachings of Aslanidis. Therefore, one of ordinary skill in the art would have been motivated to ensure that the length of the minimal length of single-stranded tails for ligation-independent cloning of nucleotides was at least 8

nucleotides in length with a reasonable expectation of success in achieving covalent joining. Further, it would have been obvious to one of ordinary skill in the art to include the linearized vector in a kit to facilitate use of the vector during the use of the vector.

Allowable Subject Matter

Claims 1-16, 18-21, 24-30 and 41-50 are allowed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Claims 1-30 and 41-50 are believed to be free of the prior art. Claims 17 and 22-23 are rejected or objected to for other reasons.

Miki teaches a method of inserting a nucleic acid fragment into a circularized vector. However, after insertion of the nucleic acid fragment, Miki does not teach melting of the hybridized cohesive circularization ends and reannealing the ends to form a circularized vector containing the nucleic acid fragment. Miki teaches ligation to seal the cohesive ends of the vector followed by digestion to form a linear vector prior to insertion of the nucleic acid fragment but does not teach sealing of the cohesive ends of the vector after insertion of the nucleic acid fragment. In claim 40, a kit is recited comprising the vector, polyethylene glycol, a buffer comprising a salt, and DNA ligase. The vector and method as taught by Miki would be facilitated by formulation of a kit containing the vector, polyethylene glycol and the buffer. However, Miki explicitly states

that DNA ligase is not used in the method. Therefore, it is not believed that the closest prior art of Miki anticipates or renders obvious the kit containing DNA ligase.

Fujimaki (Somatic Cell and Molecular Genetics, 1996 Jul, 22(4), pages 279-90) teaches the involvement of DNA topoisomerase II on nonhomologous recombination and examines the effect of topoisomerase II inhibitors on random integration of exogenous vectors into human chromosomes and demonstrates the enhancement of the frequency of transformation of colonies with the use of topoisomerase inhibitors suggesting that topoisomerase II inhibitors directly act at a nonhomologous recombination reaction, promoting the integration process of transfected vectors into human chromosomes. Topoisomerase II inhibitors directly act at a nonhomologous recombination reaction, promoting the integration process of transfected vectors into human chromosomes (see abstract).

However, neither Miki nor Fujimaki teaches the linking of a site-specific topoisomerase to the vector and they do not provide the skilled artisan any motivation to do so with a reasonable expectation of success. Therefore, it is believed that the prior art does not anticipate or render the claimed invention obvious.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stephen Siu, whose telephone number is (703) 308-7522. The Examiner can normally be reached from 7:00 a.m. to 3:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028. Papers related to this application may be submitted to Art Unit 1631 by facsimile transmission.

The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 308-0294. Please call the Examiner at (703) 308-7522 before the transmission to expedite delivery of the fax. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stephen Siu

03/09/00

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER